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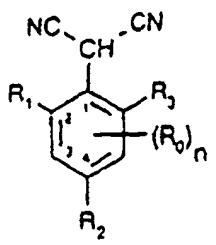
(54) Title: SUBSTITUTED ARYLMALONIC ACID DINITRILES AS INTERMEDIATES FOR THE PREPARTION OF HERBICIDES



(I)

(57) Abstract: Compounds of formula (I), as intermediates for the preparation of known, herbicidally active 3-hydroxy-4-aryl-5-oxopyrazoline derivatives. A process for their preparation and their use in the preparation of herbicides.

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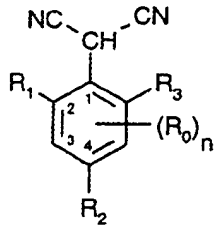
SUBSTITUTED ARYLMALONIC ACID DINITRILES AS INTERMEDIATES FOR THE PREPARATION OF HERBICIDES

The present invention relates to new substituted arylmalonic acid dinitriles as intermediates for a surprisingly advantageous overall process for the preparation of known, herbicidally active 3-hydroxy-4-aryl-5-oxopyrazoline derivatives, to a process for the preparation of those intermediates and to their use in the preparation of 3-hydroxy-4-aryl-5-oxopyrazoline derivatives.

Arylmalonic acid dinitriles and their preparation by means of palladium complexes are described, for example, in Chem. Commun. 1984, 932 and JP-A-60 197 650. Furthermore, J. Am. Chem. Soc. 121, 1473 (1999) describes the arylation of malonates by means of palladium catalysts.

New substituted arylmalonic acid dinitriles have now been found which are outstandingly suitable as intermediates for an advantageous process for the preparation of herbicidal 3-hydroxy-4-aryl-5-oxopyrazoline derivatives.

The present invention accordingly relates to compounds of formula I



(I),

wherein

R_0 is, each independently of any other, halogen, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, cyano-C_1-C_6alkyl, C_2-C_6haloalkenyl, cyano-C_2-C_6alkenyl, C_2-C_6haloalkynyl, cyano-C_2-C_6alkynyl, hydroxy, hydroxy-C_1-C_6alkyl, C_1-C_6alkoxy, nitro, amino, C_1-C_6alkylamino, di(C_1-C_6alkyl)amino, C_1-C_6alkylcarbonylamino, C_1-C_6alkylsulfonylamino, C_1-C_6alkylaminosulfonyl, C_1-C_6alkylcarbonyl, C_1-C_6alkylcarbonyl-C_1-C_6alkyl, C_1-C_6-alkoxycarbonyl-C_1-C_6alkyl, C_1-C_6alkylcarbonyl-C_2-C_6alkenyl, C_1-C_6alkoxycarbonyl, C_1-C_6alkoxycarbonyl-C_2-C_6alkenyl, C_1-C_6alkylcarbonyl-C_2-C_6alkynyl, C_1-C_6alkoxycarbonyl-C_2-C_6alkynyl, cyano, carboxyl, phenyl or an aromatic ring that contains 1 or 2 hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein the latter two

aromatic rings may be substituted by C_1-C_3alkyl, C_1-C_3haloalkyl, C_1-C_3alkoxy, C_1-C_3haloalkoxy, halogen, cyano or by nitro; or

R_0, together with the adjacent substituents R_1, R_2 and R_3, forms a saturated or unsaturated C_3-C_6hydrocarbon bridge that may be interrupted by 1 or 2 hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur and/or substituted by C_1-C_4alkyl;

R_1, R_2 and R_3 are, each independently of the others, hydrogen, halogen, C_1-C_6alkyl, C_2-C_6-alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl, C_1-C_6alkoxy-carbonyl-C_2-C_6alkenyl, C_1-C_6alkylcarbonyl-C_2-C_6alkenyl, cyano-C_2-C_6alkenyl, nitro-C_2-C_6-alkenyl, C_2-C_6haloalkynyl, C_1-C_6alkoxycarbonyl-C_2-C_6alkynyl, C_1-C_6alkylcarbonyl-C_2-C_6-alkynyl, cyano-C_2-C_6alkynyl, nitro-C_2-C_6alkynyl, C_3-C_6halocycloalkyl, hydroxy-C_1-C_6alkyl, C_1-C_6alkoxy-C_1-C_6alkyl, C_1-C_6alkylthio-C_1-C_6alkyl, cyano, C_1-C_4alkylcarbonyl, C_1-C_6-alkoxycarbonyl, hydroxy, C_1-C_{10}alkoxy, C_3-C_6alkenyloxy, C_3-C_6alkynyloxy, C_1-C_6haloalkoxy, C_3-C_6haloalkenyloxy, C_1-C_6alkoxy-C_1-C_6alkoxy, mercapto, C_1-C_6alkylthio, C_1-C_6haloalkylthio, C_1-C_6alkylsulfinyl, C_1-C_6alkylsulfonyl, nitro, amino, C_1-C_6alkylamino, di(C_1-C_6alkyl)amino or phenoxy in which the phenyl ring may be substituted by C_1-C_3alkyl, C_1-C_3haloalkyl, C_1-C_3-alkoxy, C_1-C_3haloalkoxy, halogen, cyano or by nitro;

R_2 also may be phenyl, naphthyl or a 5- or 6-membered aromatic ring that may contain 1 or 2 hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein the phenyl ring, the naphthyl ring system and the 5- or 6-membered aromatic ring may be substituted by halogen, C_3-C_8cycloalkyl, hydroxy, mercapto, amino, cyano, nitro or by formyl; and/or

the phenyl ring, the naphthyl ring system and the 5- or 6-membered aromatic ring may be substituted by C_1-C_6alkyl, C_1-C_6alkoxy, hydroxy-C_1-C_6alkyl, C_1-C_6alkoxy-C_1-C_6alkyl, C_1-C_6-alkoxy-C_1-C_6alkoxy, C_1-C_6alkylcarbonyl, C_1-C_6alkylthio, C_1-C_6alkylsulfinyl, C_1-C_6alkylsulfonyl, mono-C_1-C_6alkylamino, di(C_1-C_6alkyl)amino, C_1-C_6alkylcarbonylamino, C_1-C_6alkylcarbonyl-(C_1-C_6alkyl)amino, C_2-C_6alkenyl, C_3-C_6alkenyloxy, hydroxy-C_3-C_6alkenyl, C_1-C_6alkoxy-C_2-C_6-alkenyl, C_1-C_6alkoxy-C_3-C_6alkenyloxy, C_2-C_6alkenylcarbonyl, C_2-C_6alkenylthio, C_2-C_6alkenyl-sulfinyl, C_2-C_6alkenylsulfonyl, mono- or di-(C_2-C_6alkenyl)amino, C_1-C_6alkyl(C_3-C_6alkenyl)-amino, C_2-C_6alkenylcarbonylamino, C_2-C_6alkenylcarbonyl(C_1-C_6alkyl)amino, C_2-C_6alkynyl, C_3-C_6alkynyloxy, hydroxy-C_3-C_6alkynyl, C_1-C_6alkoxy-C_3-C_6alkynyl, C_1-C_6alkoxy-C_4-C_6-alkynyloxy, C_2-C_6alkynylcarbonyl, C_2-C_6alkynylthio, C_2-C_6alkynylsulfinyl, C_2-C_6alkynylsulfonyl, mono- or di-(C_3-C_6alkynyl)amino, C_1-C_6alkyl(C_3-C_6alkynyl)amino, C_2-C_6alkynylcarbonylamino or by C_2-C_6alkynylcarbonyl(C_1-C_6alkyl)amino; and/or

the phenyl ring, the naphthyl ring system and the 5- or 6-membered aromatic ring may be substituted by halo-substituted C_1-C_6alkyl, C_1-C_6alkoxy, hydroxy-C_1-C_6alkyl, C_1-C_6alkoxy-C_1-C_6alkyl, C_1-C_6alkoxy-C_1-C_6alkoxy, C_1-C_6alkylcarbonyl, C_1-C_6alkylthio, C_1-C_6alkylsulfinyl, C_1-C_6alkylsulfonyl, mono-C_1-C_6alkylamino, di(C_1-C_6alkyl)amino, C_1-C_6alkylcarbonylamino, C_1-C_6alkylcarbonyl(C_1-C_6alkyl)amino, C_2-C_6alkenyl, C_3-C_6alkenyloxy, hydroxy-C_3-C_6alkenyl, C_1-C_6alkoxy-C_2-C_6alkenyl, C_1-C_6alkoxy-C_3-C_6alkenyloxy, C_2-C_6alkenylcarbonyl, C_2-C_6-alkenylthio, C_2-C_6alkenylsulfinyl, C_2-C_6alkenylsulfonyl, mono- or di-(C_2-C_6alkenyl)amino, C_1-C_6-alkyl(C_3-C_6alkenyl)amino, C_2-C_6alkenylcarbonylamino, C_2-C_6alkenylcarbonyl(C_1-C_6-alkyl)amino, C_2-C_6alkynyl, C_3-C_6alkynyloxy, hydroxy-C_3-C_6alkynyl, C_1-C_6alkoxy-C_3-C_6alkynyl, C_1-C_6alkoxy-C_4-C_6alkynyloxy, C_2-C_6alkynylcarbonyl, C_2-C_6alkynylthio, C_2-C_6alkynylsulfinyl, C_2-C_6alkynylsulfonyl, mono- or di-(C_3-C_6alkynyl)amino, C_1-C_6alkyl(C_3-C_6alkynyl)amino, C_2-C_6alkynylcarbonylamino or C_2-C_6alkynylcarbonyl(C_1-C_6alkyl)amino; and/or
the phenyl ring, the naphthyl ring system and the 5- or 6-membered aromatic ring may be substituted by a radical of formula $COOR_{50}$, $CONR_{51}$, $SO_2NR_{53}R_{54}$ or SO_2OR_{55}, wherein R_{50}, R_{51}, R_{52}, R_{53}, R_{54} and R_{55} are, each independently of the others, C_1-C_6alkyl, C_2-C_6alkenyl or C_3-C_6alkynyl or halo-, hydroxy-, alkoxy-, mercapto-, amino-, cyano-, nitro-, alkylthio-, alkylsulfinyl- or alkylsulfonyl-substituted C_1-C_6alkyl, C_2-C_6alkenyl or C_3-C_6alkynyl; and
n is 0, 1 or 2.

In the above definitions, halogen is to be understood as fluorine, chlorine, bromine or iodine, preferably fluorine, chlorine or bromine.
The alkyl groups occurring in the substituent definitions are, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl or tert-butyl, and the pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl and dodecyl isomers.

Haloalkyl groups preferably have a chain length of from 1 to 6 carbon atoms. Haloalkyl is, for example, fluoromethyl, difluoromethyl, difluorochloromethyl, trifluoromethyl, chloromethyl, dichloromethyl, dichlorofluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 2-fluoroethyl, 2-chloroethyl, 2,2-difluoroethyl, 2,2-dichloroethyl, 2,2,2-trichloroethyl or pentafluoroethyl, preferably trichloromethyl, difluorochloromethyl, difluoromethyl, trifluoromethyl or dichlorofluoromethyl.

Alkoxy groups preferably have a chain length of from 1 to 6 carbon atoms. Alkoxy is, for example, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butoxy, or a pentyloxy or hexyloxy isomer, preferably methoxy, ethoxy or n-propoxy.

Haloalkoxy is, for example, fluoromethoxy, difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy, 1,1,2,2-tetrafluoroethoxy, 2-fluoroethoxy, 2-chloroethoxy or 2,2,2-trichloroethoxy.

There may be mentioned as examples of alkenyl radicals vinyl, allyl, methallyl, 1-methylvinyl, but-2-en-1-yl, pentenyl and 2-hexenyl; preferably alkenyl radicals having a chain length of from 3 to 6 carbon atoms.

There may be mentioned as examples of alkynyl radicals ethynyl, propargyl, 1-methylpropargyl, 3-butynyl, but-2-yn-1-yl, 2-methylbut-3-yn-2-yl, but-3-yn-2-yl, 1-pentynyl, pent-4-yn-1-yl and 2-hexynyl; preferably alkynyl radicals having a chain length of from 3 to 6 carbon atoms.

Suitable haloalkenyl radicals include alkenyl groups substituted one or more times by halogen, halogen being in particular bromine or iodine and especially fluorine or chlorine, for example 2- and 3-fluoropropenyl, 2- and 3-chloropropenyl, 2- and 3-bromopropenyl, 2,2-difluoro-1-methylvinyl, 2,3,3-trifluoropropenyl, 3,3,3-trifluoropropenyl, 2,3,3-trichloropropenyl, 4,4,4-trifluorobut-2-en-1-yl and 4,4,4-trichlorobut-2-en-1-yl. Preferred alkenyl radicals substituted once, twice or three times by halogen are those having a chain length of from 3 to 6 carbon atoms. The alkenyl groups may be substituted by halogen at saturated or unsaturated carbon atoms.

Alkoxyalkyl groups have preferably from 1 to 6 carbon atoms. Alkoxyalkyl is, for example, methoxymethyl, methoxyethyl, ethoxymethyl, ethoxyethyl, n-propoxymethyl, n-propoxyethyl, isopropoxymethyl or isopropoxyethyl.

Haloalkoxy is, for example, fluoromethoxy, difluoromethoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy, 1,1,2,2-tetrafluoroethoxy, 2-fluoroethoxy, 2-chloroethoxy or 2,2,2-trichloroethoxy.

Alkenyloxy is, for example, allyloxy, methallyloxy or but-2-en-1-yloxy.

Suitable haloalkenyloxy groups include alkenyloxy groups substituted one or more times by halogen, halogen being in particular bromine or iodine and especially fluorine or chlorine, for example 2- and 3-fluoropropenyloxy, 2- and 3-chloropropenyloxy, 2- and 3-bromopropenyloxy, 2,3,3-trifluoropropenyloxy, 2,3,3-trichloropropenyloxy, 4,4,4-trifluorobut-2-en-1-yloxy and 4,4,4-trichlorobut-2-en-1-yloxy.

Alkynyloxy is, for example, propargyloxy or 1-methylpropargyloxy.

Suitable cycloalkyl substituents contain from 3 to 8 carbon atoms and are, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl. They may be substituted one or more times by halogen, preferably fluorine, chlorine or bromine.

Alkylcarbonyl is especially acetyl or propionyl.

Alkoxycarbonyl is, for example, methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, isopropoxycarbonyl or a butoxycarbonyl, pentyloxycarbonyl or hexyloxycarbonyl isomer, preferably methoxycarbonyl or ethoxycarbonyl.

Alkylthio groups preferably have a chain length of from 1 to 6 carbon atoms. Alkylthio is, for example, methylthio, ethylthio, propylthio, butylthio, pentylthio or hexylthio, or a branched isomer thereof, but is preferably methylthio or ethylthio.

Haloalkylthio is, for example, 2,2,2-trifluoroethylthio or 2,2,2-trichloroethylthio.

Alkylsulfinyl is, for example, methylsulfinyl, ethylsulfinyl, n-propylsulfinyl, isopropylsulfinyl, n-butylsulfinyl, isobutylsulfinyl, sec-butylsulfinyl or tert-butylsulfinyl, preferably methylsulfinyl or ethylsulfinyl.

Alkylsulfonyl is, for example, methylsulfonyl, ethylsulfonyl, n-propylsulfonyl, isopropylsulfonyl, n-butylsulfonyl, isobutylsulfonyl, sec-butylsulfonyl or tert-butylsulfonyl, preferably methylsulfonyl or ethylsulfonyl.

Alkylamino is, for example, methylamino, ethylamino, n-propylamino, isopropylamino or a butyl-, pentyl- or hexyl-amine isomer.

Dialkylamino is, for example, dimethylamino, methylethylamino, diethylamino, n-propyl-methylamino, dibutylamino or diisopropylamino.

Alkylthioalkyl is, for example, methylthiomethyl, methylthioethyl, ethylthiomethyl, ethylthio-ethyl, n-propylthiomethyl, n-propylthioethyl, isopropylthiomethyl or isopropylthioethyl.

Phenyl and naphthyl in the definition of R_2 and phenoxy in the definition of R_1, R_2 and R_3 may be in substituted form, in which case the substituents may, as desired, be in the ortho-, meta- and/or para-position and, in the case of the naphthyl ring system, in addition in the 5-, 6-, 7- and/or 8-position.

Examples of suitable 5- or 6-membered aromatic rings that contain 1 or 2 hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur in the definition of R_0 and R_2 are pyrrolidyl, pyridyl, pyrimidyl, triazinyl, thiazolyl, triazolyl, thiadiazolyl, imidazolyl, oxazolyl, isoxazolyl, pyrazinyl, furyl, thienyl, pyrazolyl, benzoxazolyl, benzothiazolyl, quinoxalyl, indolyl and quinolyl. These heteroaromatic radicals may, in addition, be substituted.

Meanings corresponding to those given hereinbefore can also be ascribed to substituents in composite definitions, such as, for example, alkoxy-alkoxy, alkyl-sulfonylamino, alkyl-aminosulfonyl, phenyl-alkyl, naphthyl-alkyl and heteroaryl-alkyl.

In the definitions for alkylcarbonyl and alkoxycarbonyl, the carbon atom of the carbonyl is not included in the upper and lower limits given for the number of carbons in each particular case.

Preference is given to compounds of formula I wherein n is as defined for formula I; R_0 is, each independently of any other, halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, hydroxy, C_1-C_6alkoxy, nitro, amino, C_1-C_6alkylamino, di(C_1-C_6alkyl)amino, C_1-C_6alkylcarbonylamino, C_1-C_6alkyl-sulfonylamino, C_1-C_6alkylaminosulfonyl, C_1-C_4alkylcarbonyl, C_1-C_6alkoxycarbonyl or

carboxyl; and R_1, R_2 and R_3 are, each independently of the others, hydrogen, halogen, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, C_1-C_6-haloalkyl, C_2-C_6haloalkenyl, C_2-C_6haloalkynyl, C_3-C_6halocycloalkyl, C_1-C_6alkoxy-C_1-C_6alkyl, C_1-C_6alkylthio-C_1-C_6alkyl, cyano, C_1-C_4alkylcarbonyl, C_1-C_6alkoxycarbonyl, hydroxy, C_1-C_{10}alkoxy, C_3-C_6alkenyloxy, C_3-C_6alkynyloxy, C_1-C_6haloalkoxy, C_3-C_6haloalkenyloxy, C_1-C_6alkoxy-C_1-C_6alkoxy, mercapto, C_1-C_6alkylthio, C_1-C_6haloalkylthio, C_1-C_6alkylsulfinyl, C_1-C_6alkylsulfonyl, nitro, amino, C_1-C_4alkylamino or di(C_1-C_4alkyl)amino.

Preference is given also to compounds of formula I wherein R_1, R_2 and R_3 are, each independently of the others, hydrogen, halogen, C_1-C_4alkyl, C_1-C_4haloalkyl, C_2-C_4alkenyl, C_2-C_4haloalkenyl, C_2-C_4alkynyl, C_3-C_6cycloalkyl, C_1-C_4alkylcarbonyl, C_1-C_6alkoxycarbonyl, hydroxy, C_1-C_4alkoxy, C_3- or C_4-alkenyloxy, C_3- or C_4-alkynyloxy, C_1-C_4haloalkoxy, nitro or amino.

Preference is given also to compounds of formula I wherein R_1 is C_2-C_6alkyl.

Likewise preferred are compounds of formula I wherein n is 0.
Of those, special preference is given to compounds of formula I wherein R_1 is C_2-C_4alkyl, C_1-C_4alkoxy, C_2-C_4alkynyl or C_3-C_6cycloalkyl and R_3 is C_1-C_4alkyl, C_1-C_4alkoxy, C_2-C_4alkynyl or C_3-C_6cycloalkyl.

Likewise preferred are compounds of formula I wherein R_1 is C_2-C_6alkynyl.

Preference is given to those compounds of formula I wherein R_1 and R_3 are, each independently of the other, C_2-C_6alkyl, C_2-C_6alkynyl, C_1-C_{10}alkoxy or C_3-C_6cycloalkyl. Of those, special preference is given to compounds wherein R_1 is C_2-C_6alkyl and R_3 is C_2-C_6alkyl, C_2-C_6alkynyl or C_1-C_{10}alkoxy.

Chem. Commun. 1984, 932 and JP-A-60 197 650 describe a palladium-catalysed synthesis of arylmalonic dinitriles, in yields of from 56 to 95 %, by C-C linkage of aryl halides - unsubstituted or mono-substituted in the 2- or 4-position - with the malonic dinitrile anion. Mention is made, by way of example, of $(PPh_3)_2PdCl_2$ and $Pd(PPh_3)_4$ as palladium complexes and of tetrahydrofuran as reaction medium, JP-A-60 197 650, which is drafted with a broader scope, also mentioning bis(trialkylphosphine)- and bis(trialkoxy- and

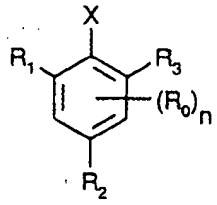
triphenoxy-phosphine)-palladium(II) chloride complexes and, as reaction media, ethylene glycol dimethyl ether and dimethylformamide. In both documents, the only aryl halides specifically mentioned are unsubstituted or mono-substituted aryl iodides and a bromo-benzene activated in the 4-position by a cyano group.

It has now been found, surprisingly, that the C-C linkage of malonic acid dinitrile with a large group of mono- or poly-substituted aryl derivatives additionally containing a leaving group is feasible in various reaction media in the presence of a wide variety of palladium(II) or palladium(0) complexes in high product yields and purities.

The present process is distinguished by:
a) wide variability of reaction media and reaction conditions,
b) high volume concentrations of the reactants (up to 10%),
c) a large number of suitable palladium catalysts,
d) widely – especially in the 2- and 6-positions – substituted phenyl derivatives as starting compounds, having various leaving groups, including sterically hindered (low-reactivity) leaving groups,
e) easy accessibility of the starting compounds,
f) the use of catalysts that are either commercially available or easily prepared 'in situ' from commercially available palladium salts, such as, for example, palladium(II) chloride solution (20 %) in concentrated hydrochloric acid with the addition of dimethyl acetamide (DMA) as solubility promoter, and corresponding ligands,
g) a simple reaction procedure, such as, for example, reaction of the 'in situ'-generated malonic acid dinitrile anion and palladium catalyst with an aryl halide or arylsulfonate,
h) simple and effective working-up methods that yield the C-C linkage products of formula I in a high degree of purity (Example P17),
i) generally very high product yields, and
j) economic and ecological advantages derived from the fact that the process can be used as a partial step in a continuous reaction procedure for the preparation of 3-hydroxy-4-aryl-5-oxopyrazoline derivatives of formula III (Reaction Scheme 3).

The present preparation process is therefore suitable especially for the large-scale preparation of arylmalonic acid dinitrile derivatives of formula I.

The process according to the invention for the preparation of compounds of formula I comprises reacting a compound of formula II

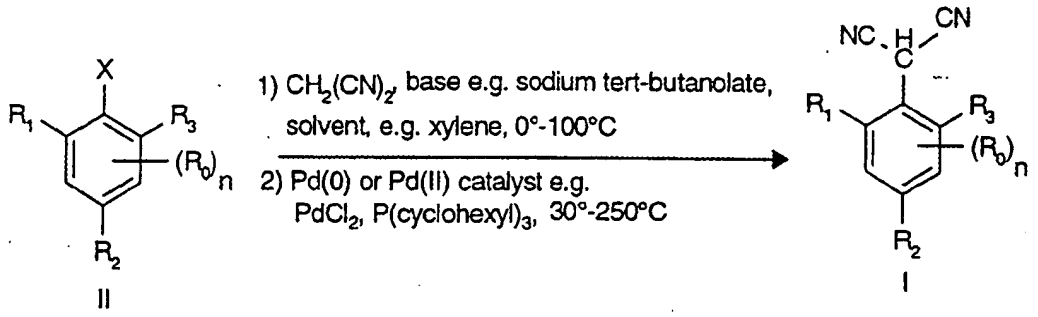


(II),

wherein R_0, R_1, R_2, R_3 and n are as defined for formula I and X is a leaving group, with the malonic acid dinitrile anion in an inert solvent in the presence of a palladium catalyst. The malonic acid dinitrile anion is preferably prepared 'in situ' from malonic acid dinitrile and a base.

The preparation of compounds of formula I is illustrated in the following Reaction Scheme 1.

Reaction Scheme 1



According to Reaction Scheme 1, the compounds of formula I are obtained from the compounds of formula II by adding the latter, in a first reaction step, at a temperature of from 0° to 100°C, to a prepared solution of malonic acid dinitrile in a suitable solvent, for example an aromatic hydrocarbon, an ether or dimethyl sulfoxide, e.g. xylene or tetrahydrofuran, and in the presence of a base, for example an alkali metal alcoholate, e.g. sodium tert-butanolate, together with a palladium catalyst, for example a separately prepared palladium catalyst, for example, bis(tricyclohexylphosphine)palladium(II) dichloride ($Pd(PCy_3)_2Cl_2$). The coupling reaction is started by heating the resulting reaction solution to a temperature of from 30° to 250°C, depending on the solvent used.

Suitable leaving groups X for the C-C linkage reaction of the compound of formula II with the malonic acid dinitrile anion in the presence of palladium catalysts are halogen, $R_{10}S(O)_2O$- (wherein R_{10} is C_1-C_4alkyl, preferably methyl, C_1-C_4haloalkyl, preferably halomethyl or n-C_4F_9, aryl, preferably phenyl, or phenyl mono- to tri-substituted by halogen, methyl or by halomethyl) and mono-, di- or tri-arylmethoxy.

The aryl radicals of the mono-, di- and tri-arylmethoxy groups are preferably phenyl radicals, which may be substituted for example by methyl from once to three times, the substituents preferably being in the 2-, 4- and/or 6-position of the phenyl ring.
Examples of such leaving groups are methylsulfonyloxy (mesylate), trifluoromethylsulfonyloxy (triflate), *p*-tolylsulfonyloxy (tosylate), $CF_3(CF_2)_3S(O)_2O$- (nonaflate), diphenylmethoxy, di(methylphenyl)methoxy, triphenylmethoxy (trityl) and tri(methylphenyl)methoxy.

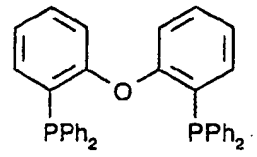
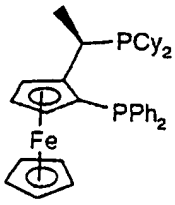
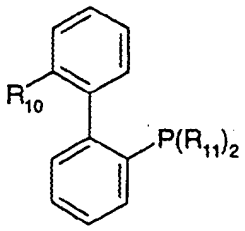
Special preference is given to those leaving groups wherein X is chlorine, bromine, iodine, $CF_3S(O)_2O$- (triflate), $CF_3(CF_2)_3S(O)_2O$- (nonaflate), *p*-tolyl-$S(O)_2O$- (tosylate), $(C_6H_5)_2CHO$-, $(CH_3$-$C_6H_4)_2CHO$-, $(C_6H_5)_3CO$- (trityl) or $(CH_3$-$C_6H_4)_3CO$-. Of those, preference is given more especially to leaving groups wherein X is chlorine, bromine or iodine.

The palladium catalysts suitable for the C-C linkage reaction of the compound of formula II with the malonic acid dinitrile anion are generally palladium(II) or palladium(0) complexes, such as, for example, palladium(II) dihalides, palladium(II) acetate, palladium(II) sulfate, bis(triphenylphosphine)palladium(II) dichloride, bis(tricyclopentylphosphine)palladium(II) dichloride, bis(tricyclohexylphosphine)palladium(II) dichloride, bis(dibenzylideneacetone)-palladium(0) or tetrakis(triphenylphosphine)palladium(0).

In an especially advantageous variant of the process according to the invention, the palladium catalyst can also be prepared 'in situ' from palladium(II) or palladium(0) compounds as a result of complexing with the desired ligands, for example by placing the palladium(II) salt to be complexed, e.g. palladium(II) dichloride ($PdCl_2$) or palladium(II) acetate ($Pd(OAc)_2$), together with the desired ligand e.g. triphenylphosphine (PPh_3) or tricyclohexylphosphine (PCy_3) together with the selected solvent, malonic acid dinitrile and base. Palladium(II) dichloride, as a reasonably priced palladium salt, can advantageously also be used in the form of a 20 % $PdCl_2$-solution in concentrated hydrochloric acid and in the presence of dimethyl acetamide (DMA) as solubility promoter (Examples P4 and P17),

whereas the more expensive palladium(II) diacetate is substantially soluble, for example, in tetrahydrofuran. The desired ligand is advantageously added to the reaction medium in a molar excess of up to 10, based on the palladium salt. Heating the reaction medium then causes the palladium(II) or palladium(0) complex desired for the C-C coupling reaction to form 'in situ', which then starts the C-C coupling reaction.

Examples of suitable ligands for palladium(II) and palladium(0) complexes are trimethylphosphine, triethylphosphine, tris(tert-butyl)phosphine, tricyclopentylphosphine, tricyclohexylphosphine (PCy_3), tri(methylcyclohexyl)phosphine, methyl(tetramethylene)phosphine, tert-butyl(pentamethylene)phosphine, triphenylphosphine (PPh_3), tri(methylphenyl)phosphine, 1,2-(diphenylphosphino)cyclohexane, 1,2-(diphenylphosphino)cyclopentane, 2,2'-(diphenylphosphino)biphenyl, 1,2-bis(diphenylphosphino)ethane, 1,3-bis(diphenylphosphino)propane, 1,4-bis(diphenylphosphino)butane, 3,4-bis(diphenylphosphino)-pyrrolidine, 2,2'-(diphenylphosphino)-bisnaphthalene (BINAP), 1,1'-bis(diphenylphosphino)-ferrocene, 1,1'-bis(di-tert-butylphosphino)ferrocene, diphenyl ether bis-diphenylphosphine

( = dpephos),  and  , wherein

R_{10} is hydrogen or dimethylamino, and R_{11} is cyclohexyl or tert-butyl. These latter electron-rich and sterically bulky diphenyl derivatives are especially suitable phosphine ligands for the preparation of the present specific palladium catalysts, the so-called Buchwald catalysts. These, in turn, are especially suitable for the C-C linkage according to the invention of malonic acid dinitrile with polysubstituted aryl derivatives in combination with alkali metal hydrides or alkali metal phosphates as the base and toluene or xylenes as solvent.

The said ligands and palladium complexes are known and are described in a number of references in the literature, such as, for example, J. Am. Chem. Soc. 121, 4369-4378 (1999), EP-A-0 564 406, EP-A-0 646 590 and 'Palladium Reagents and Catalysts', Editor J. Tsuji, John Wiley & Sons, 1995.

Palladium(0) complexes with mono- and bi-dentate, tertiary or di-tertiary amines, phosphines and arsines as ligands are generally used. The N-, P- and/or As atoms of those ligands may be substituted by identical or different, straight-chain or branched aliphatic radicals containing from 1 to 18 carbon atoms, preferably from 1 to 12 carbon atoms and especially from 1 to 8 carbon atoms.
Also suitable are unsubstituted or C_1-C_4alkyl-substituted C_5-C_7cycloalkyl, unsubstituted or C_1-C_4alkyl-substituted C_6-C_{10}aryl radicals, especially phenyl and alkylphenyl radicals, and the benzyl radical, which is unsubstituted or substituted by C_1-C_4alkyl.
Two of the aliphatic radicals bound to the hetero atoms N, P and/or As may together form an unsubstituted or C_1-C_4alkyl-substituted C_4- or C_5-hydrocarbon bridge, thereby forming, together with the hetero atom, a 5- or 6-membered heterocyclic ring.
In the case of bidentate ligands, two of the N, P and/or As atoms are (bivalently) linked by way of an aliphatic, unsubstituted or C_1-C_4alkyl-substituted C_2-C_5hydrocarbon chain. The aliphatic, bivalent hydrocarbon chain can optionally be interrupted by 1 or 2 hetero atoms, such as, for example O, N and/or S and/or may be part of a ring or ring system.
Preference is given to phosphine ligands, especially basic and sterically bulky phosphine ligands, such as, for example, tricyclohexyl- or tri-tert-butyl-phosphine, because the concentration of the corresponding palladium complexes can then be significantly reduced (by a factor of from 3 to 10) without loss of their catalytic activity.

The palladium catalysts are used in an amount of from 0.001 to 50 mol %, preferably in an amount of from 0.01 to 10 mol % and especially in an amount of from 0.1 to 3 mol %, based on the compound of formula II.

Suitable solvents for the formation of the malonic acid dinitrile anion (Step 1 in Reaction Scheme 1) and for the palladium-catalysed C-C linkage reaction with the compound of formula II (Step 2 in Reaction Scheme 1) are aliphatic, cycloaliphatic or aromatic hydrocarbons, such as, for example, pentane, hexane, petroleum ether, cyclohexane, methylcyclohexane, benzene, toluene and xylenes, aliphatic halohydrocarbons, such as, for example, methylene chloride, chloroform and di- or tetrachlorethane, nitriles, such as, for example, acetonitrile, propionitrile and benzonitrile, ethers, such as, for example, diethyl ether, dibutyl ether, tert-butyl methyl ether, ethylene glycol dimethyl ether, ethylene glycol diethyl ether, diethylene glycol dimethyl ether, tetrahydrofuran and dioxane, alcohols, such as, for example, methanol, ethanol, propanol, butanol, ethylene glycol, diethylene glycol,

ethylene glycol monomethyl or monoethyl ether and diethylene glycol monomethyl or monoethyl ether, ketones, such as, for example, acetone and methyl isobutyl ketone, esters or lactones, such as, for example, ethyl or methyl acetate and valerolactone, N-substituted lactams, such as, for example, N-methylpyrrolidone (NMP), amides, such as, for example, N,N-dimethylformamide (DMF) and dimethyl acetamide (DMA), acyclic ureas, such as, for example, N,N'-dimethylethylene urea (DMEU), sulfoxides, such as, for example, dimethyl sulfoxide or mixtures of these solvents. Of these, special preference is given to aromatic hydrocarbons, ethers and dimethyl sulfoxide.

Suitable bases for the preparation of the malonic acid dinitrile anion are weakly nucleophilic bases, such as, for example, tri-alkali metal phosphates, alkali metal and alkaline earth metal hydrides, alkali metal and alkaline earth metal amides and alkali metal alcoholates, for example tripotassium phosphate, potassium or sodium tert-butanolate, lithium diisopropyl-amide (LDA) and potassium or sodium hydride. The said bases are preferably used in an excess of from 2 to 10 equivalents, based on malonic acid dinitrile.
Base/solvent combinations especially suitable for producing the malonic acid dinitrile anions (Step 1 in Reaction Scheme 1) are, for example, alkali metal alcoholates in aliphatic, cycloaliphatic or aromatic hydrocarbons, for example sodium tert-butanolate in xylene.
Combinations of palladium catalysts and leaving groups X in compounds of formula II that are especially suitable for the C-C linkage reaction (Step 2 in Reaction Scheme 1) are palladium(II)-bis(tricycloalkylphosphine) dihalides and halogens, for example palladium(II)-bis(tricyclohexylphosphine) dichloride and bromide.

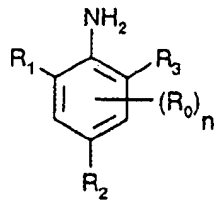
Advantageously, the formation of the malonic acid dinitrile anion is carried out at reaction temperatures of from 0° to 100°C, preferably at temperatures of from 20° to 80°C, and the reaction thereof with the compound of formula II in the presence of the palladium catalyst is carried out at reaction temperatures of from 30° to 250°C, preferably from 50° to 200°C and especially from 80° to 160°C, depending on the reaction medium and reaction pressure used.

The C-C coupling reaction of the malonic acid dinitrile anion with a compound of formula II may optionally be carried out at an elevated pressure of from 1.1 to 10 bar. That process in a closed system at an elevated pressure is suitable especially for reactions at temperatures

above the boiling point of the solvent used, for example at temperatures of 140°C in the case of toluene.

Because of the very small amount of (readily decomposable) palladium catalyst used for the C-C linkage reaction, it is advantageously introduced into the reaction mixture under an inert gas atmosphere and at the very end of the sequence of the reagent addition (Step 2 in Reaction Scheme 1) (Example P17).

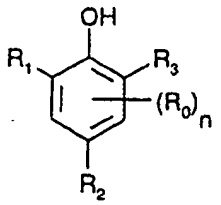
The compounds of formula II wherein X is, for example, halogen are known or can be prepared by known methods, such as, for example, the Sandmeyer reaction, from the corresponding substituted anilines of formula VIII



(VIII),

wherein R_0, R_1, R_2, R_3 and n are as defined for formula I, *via* the corresponding diazonium salts.

The compounds of formula II wherein X is, for example, $R_{10}S(O)_2O$- or mono-, di- or tri-arylmethoxy can be prepared by standard methods from the corresponding phenols of formula IX



(IX),

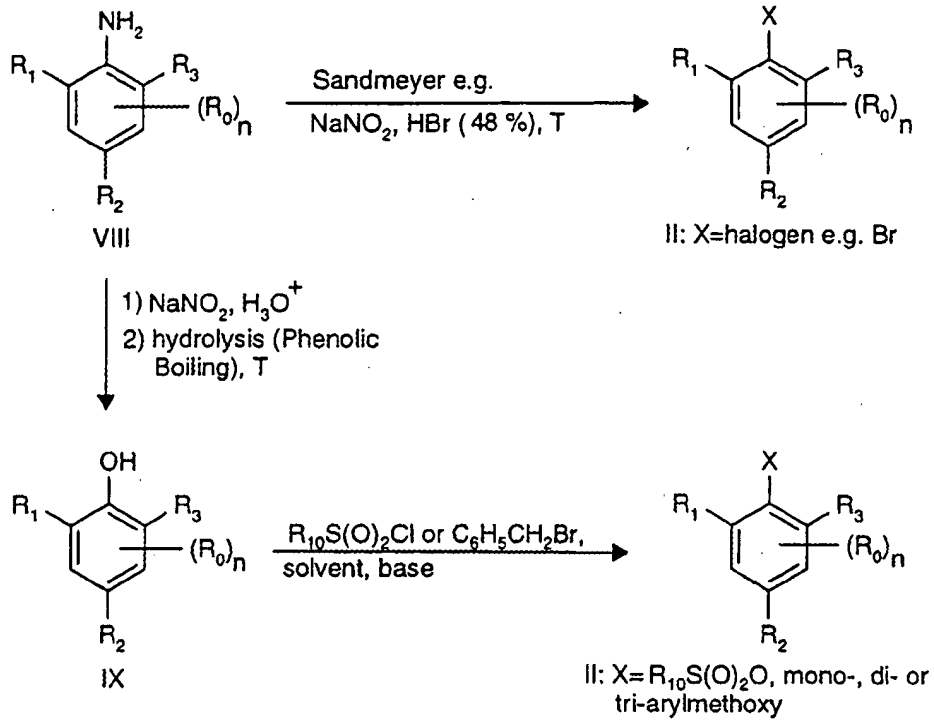
wherein R_0, R_1, R_2, R_3 and n are as defined hereinbefore.

The substituted anilines of formula VIII either are known or can be prepared by known methods, for example as described in EP-A-0 362 667 *via* alkylation of anilines using olefins.

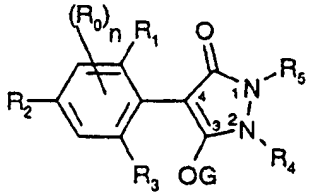
Similarly, the substituted phenols of formula IX either are known or can be prepared, for example, from the corresponding anilines of formula VIII or diazonium salts thereof by so-called Phenolic Boiling.

The following Reaction Scheme 2 illustrates the possible methods of preparing the compounds of formula II.

Reaction Scheme 2



The present substituted aryl dinitriles of formula I are in particular used as intermediates for the preparation of substituted 3-hydroxy-4-aryl-5-oxopyrazoline derivatives of formula III



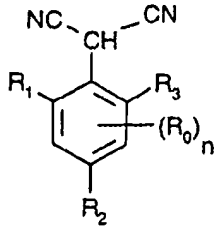
(III),

wherein R_0, R_1, R_2, R_3 and n are as defined for formula I, and R_4 and R_5 are, each independently of the other, hydrogen, C_1-C_{12}alkyl, C_1-C_{12}haloalkyl, C_2-C_8alkenyl, C_2-C_8-alkynyl, C_1-C_{10}alkoxy-C_1-C_8alkyl, poly-C_1-C_{10}alkoxy-C_1-C_8alkyl, C_1-C_{10}alkylthio-C_1-C_8alkyl, C_3-C_8cycloalkyl, C_3-C_8halocycloalkyl, 4- to 8-membered heterocyclyl, phenyl, α- or β-naphthyl, phenyl-C_1-C_6alkyl, α- or β-naphthyl-C_1-C_6alkyl, 5- or 6-membered heteroaryl or 5- or 6-membered heteroaryl-C_1-C_6alkyl, wherein the aromatic and heteroaromatic rings

may be substituted by halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, nitro or by cyano, or

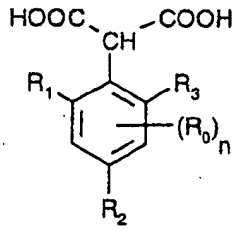
R_4 and R_5, together with the nitrogen atoms to which they are bonded, form a saturated or unsaturated, 5- to 8-membered heterocyclic ring that 1) may be interrupted by oxygen, sulfur or by -NR_7- and/or substituted by halogen, C_1-C_{10}alkyl, C_1-C_{10}haloalkyl, hydroxy, C_1-C_6alkoxy, C_1-C_6alkoxy-C_1-C_6alkoxy, C_1-C_6haloalkoxy, mercapto, C_1-C_6alkylthio, C_3-C_7cycloalkyl, heteroaryl, heteroaryl-C_1-C_6alkyl, phenyl, phenyl-C_1-C_6alkyl or by benzyloxy, wherein the phenyl rings of the last 3 substituents may in turn be substituted by halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy or by nitro, and/or 2) may contain a fused or spiro-bound alkylene or alkenylene chain having from 2 to 6 carbon atoms that is optionally interrupted by oxygen or by sulfur, or at least one ring atom of the saturated or unsaturated heterocyclic ring bridges that alkylene or alkenylene chain; R_7 is hydrogen, C_1-C_4alkyl, C_1-C_6alkylcarbonyl, C_1-C_6alkylsulfonyl, C_3-C_6alkenyl or C_3-C_6alkynyl; and G is hydrogen, a metal ion equivalent or an ammonium, sulfonium or phosphonium ion, by either

a) hydrolysing a compound of formula I



(I),

wherein R_0, R_1, R_2, R_3 and n are as defined hereinbefore, to form a compound of formula IV



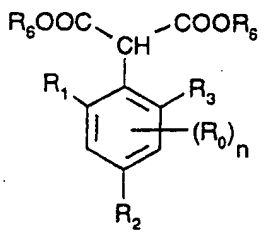
(IV),

and then, by known standard procedures, in a manner known *per se*, either

a_1) esterifying that compound with an alcohol of formula VII

R_6-OH (VII),

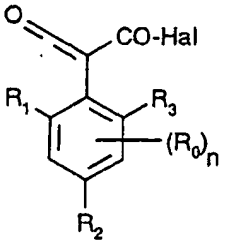
wherein R_6 is C_1-C_6alkyl, C_1-C_6haloalkyl or benzyl, to form the arylmalonic acid ester of formula V



(V),

wherein R_0, R_1, R_2, R_3, R_6 and n are as defined hereinbefore, or

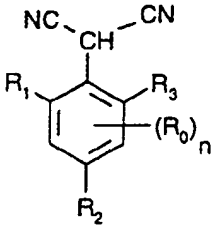
a_2) converting that compound, using an acid halide, into the halocarbonylketene of formula X



(X),

wherein R_0, R_1, R_2, R_3 and n are as defined hereinbefore and Hal is halogen, or

b) subjecting a compound of formula I

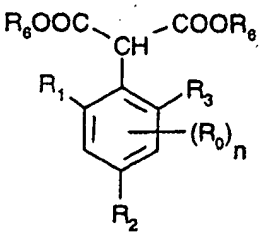


(I),

wherein R_0, R_1, R_2, R_3 and n are as defined hereinbefore, to alcoholysis directly with a compound of formula VII

R_6-OH (VII),

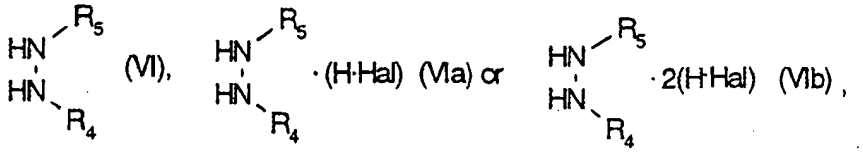
wherein R_6 is as defined hereinbefore, to form a compound of formula V



(V),

wherein R_0, R_1, R_2, R_3, R_6 and n are as defined hereinbefore,

and then reacting that compound of formula V or a compound of formula X (variant a followed by a_2) with a compound of formula VI, VIa or VIb



(VI), (VIa) or (VIb),

wherein R_4 and R_5 are as defined hereinbefore and H•Hal is a hydrogen halide, in an inert organic solvent, optionally in the presence of a base, and then optionally converting the resulting compound of formula III wherein G is a metal ion equivalent or an ammonium cation, by salt conversion into the corresponding salt of formula III wherein G is a sulfonium or phosphonium cation, or by treatment with a Brönsted acid into the corresponding compound of formula III wherein G is hydrogen.

Meanings corresponding to those given for compounds of formula I can be ascribed to the halogen, alkyl, haloalkyl, alkenyl, alkynyl, alkoxyalkyl, alkylthioalkyl, cycloalkyl and halocycloalkyl radicals present in the radicals R_4 and R_5 in compounds of formula III.

Polyalkoxy-alkyl is, for example, methoxymethoxy-methyl, ethoxymethoxy-methyl, ethoxy-ethoxy-methyl, n-propoxyethoxy-methyl, isopropoxyethoxy-methyl, methoxymethoxy-ethyl, ethoxymethoxy-ethyl, ethoxyethoxy-ethyl, n-propoxyethoxy-methyl, n-propoxyethoxy-ethyl, isopropoxyethoxy-methyl, isopropoxyethoxy-ethyl or $(ethoxy)_3$-ethyl.

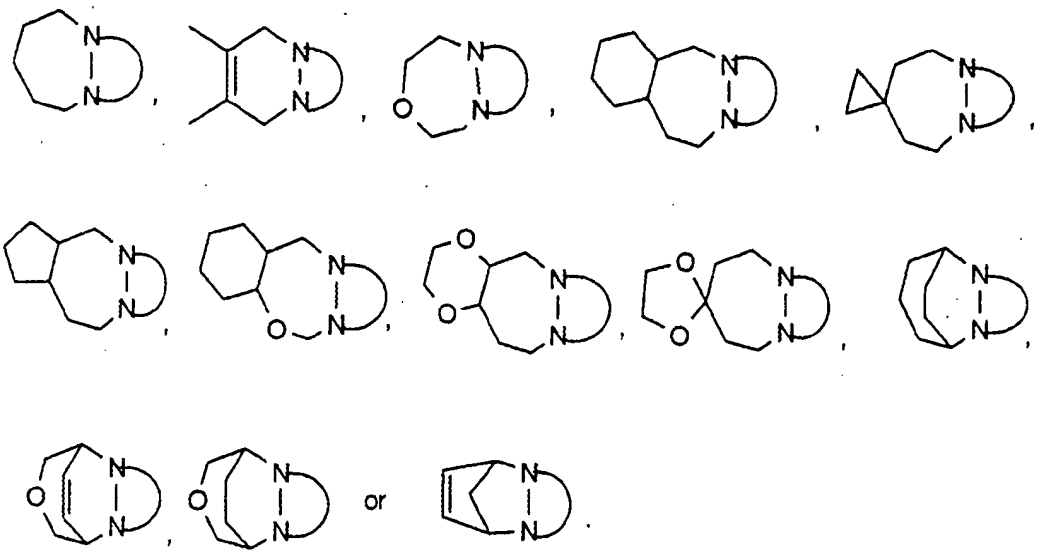
Phenyl and naphthyl may be in substituted form, in which case the substituents may, as desired, be in the ortho-, meta- and/or para-position and, in the case of the naphthyl ring system, in addition in the 5-, 6-, 7- and/or 8-position. Preferred positions for the substituents are the ortho- and para-position to the ring attachment point. Phenyl and naphthyl substituents are, for example, C_1-C_4alkyl, halogen, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6halo-alkoxy, nitro, cyano, amino, C_1-C_4alkylamino and di(C_1-C_4alkyl)amino.
Heterocyclyl radicals in the definition of R_4 and R_5 are preferably 4- to 8-membered rings that contain 1 or 2 hetero atoms, such as, for example, N, S and/or O. They are usually saturated.

Heteroaryl radicals in the definition of R_4 and R_5 are usually 5- or 6-membered aromatic heterocycles that preferably contain from 1 to 3 hetero atoms, such as N, S and/or O.

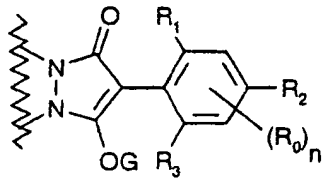
Examples of suitable heterocyclyl and heteroaryl radicals are pyrrolidyl, piperidyl, pyranyl, dioxanyl, azetidyl, oxetanyl, pyridyl, pyrimidyl, triazinyl, thiazolyl, triazolyl, thiadiazolyl, imidazolyl, oxazolyl, isoxazolyl, pyrazinyl, furyl, thienyl, morpholyl, piperazinyl, pyrazolyl, benzoxazolyl, benzothiazolyl, quinoxalyl, indolyl and quinolyl. These heterocycles and heteroaromatic radicals may, in addition, be substituted, for example by halogen, C_1-C_6alkyl, C_1-C_6alkoxy, C_1-C_6haloalkyl, C_1-C_6halogenalkoxy, nitro or by cyano.

Metal ion equivalents, such as, for example, alkali metal or alkaline earth metal ions, and ammonium ions, for the substituent G in the compound of formula III are, for example, the cations of sodium, potassium, magnesium, calcium and ammonium, such as, for example, triethylammonium and methylammonium. Sulfonium cations include, for example, tri(C_1-C_4-alkyl)sulfonium cations and can be obtained, for example, by converting the corresponding alkali metal salts, e.g. with the aid of a cation exchanger.

The substituent definition according to which "R_4 and R_5, together with the nitrogen atoms to which they are bonded, form a saturated or unsaturated, 5- to 8-membered heterocyclic ring that 1) may be interrupted by oxygen, sulfur or by -NR_7- and/or substituted by halogen, C_1-C_{10}alkyl, C_1-C_{10}haloalkyl, hydroxy, C_1-C_6alkoxy, C_1-C_6alkoxy-C_1-C_6alkoxy, C_1-C_6haloalkoxy, mercapto, C_1-C_6alkylthio, C_3-C_7cycloalkyl, heteroaryl, heteroaryl-C_1-C_6alkyl, phenyl, phenyl-C_1-C_6alkyl or by benzyloxy, wherein the phenyl rings of the last 3 substituents may in turn be substituted by halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy or by nitro, and/or 2) may contain a fused or spiro-bound alkylene or alkenylene chain having from 2 to 6 carbon atoms that is optionally interrupted by oxygen or by sulfur, or at least one ring atom of the saturated or unsaturated heterocyclic ring bridges that alkylene or alkenylene chain" signifies, for example, the following heterocyclic ring systems in the compounds of formula III:



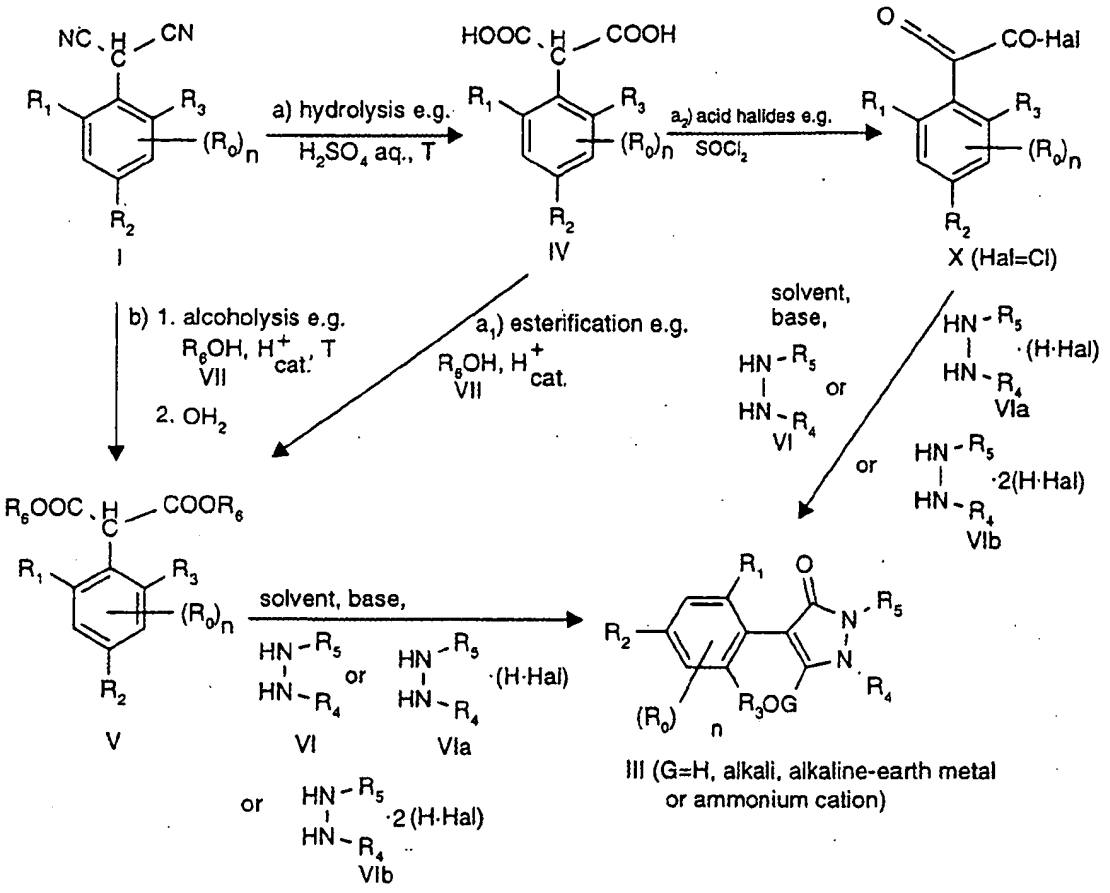
In the above polycyclic ring systems, the abbreviated representation  denotes

the group  .

The 5- to 8-membered heterocyclic rings that the substituents R_4 and R_5 together may form and the fused or spiro-bound alkylene or alkenylene chains having from 2 to 6 carbon atoms may, accordingly, be interrupted once or twice by hetero atoms.

The use of compounds of formula I in the preparation of 3-hydroxy-4-aryl-5-oxopyrazoline derivatives of formula III is illustrated in Reaction Scheme 3.

Reaction Scheme 3



The hydrolysis of the arylmalonic dinitriles of formula I to form the arylmalonic acids of formula IV (Reaction Scheme 3, Route a) is carried out according to known standard procedures, such as, for example, by heating at about 50°C for several hours in dilute sulfuric acid.

The subsequent esterification of the resulting arylmalonic acid of formula IV to form the arylmalonic ester of formula V is carried out according to known standard procedures, for example by reaction with an excess of an alcohol of formula VII in the presence of catalytic amounts of acid (Reaction Scheme 3, Route a_1).

Alternatively, the arylmalonic acids of formula IV can also be converted into the corresponding halocarbonylketenes of formula X, wherein R_0, R_1, R_2, R_3 and n are as defined hereinbefore and Hal is halogen, preferably chlorine or bromine, analogously to WO 97/02243 , using an acid halide, such as, for example, oxalyl chloride, thionyl chloride, thionyl bromide,

phosphorus trichloride, phosphorus pentachloride or phosgene, optionally in the presence of a catalyst, such as, for example, diethylformamide or triphenylphosphine and optionally in the presence of a base, such as, for example, pyridine or triethylamine, at temperatures of from -20°C to 200°C (Reaction Scheme 3, Route a_2).

The arylmalonic dinitriles of formula I can also be converted directly into the arylmalonic acid esters of formula V *via* alcoholysis (Pinner reaction) with an alcohol of formula VII in the presence of catalytic amounts of acid, optionally at an elevated temperature, and subsequent working-up in an aqueous medium (Reaction Scheme 3, Route b). Such alcoholysis reactions are described, for example, in Chem. Rev. 61, 179 (1961).

The condensation of the arylmalonic acid esters of formula V with a hydrazine derivative of formula VI or a salt thereof of formula VIa or VIb is carried out in a manner analogous to that described, for example, in WO 92/16510 or WO 97/02243 in an organic solvent, such as, for example, xylene, optionally in the presence of a base, such as, for example, triethylamine, and yields the desired target compound of formula III (G = H) or a salt thereof (G = alkali metal or alkaline earth metal ion equivalent or ammonium ion) depending on the working-up method and on the base used in the condensation reaction. The corresponding sulfonium and phosphonium salts can be produced by means of salt conversion, for example using a cation exchanger.

The condensation reaction of the compounds of formula V with compounds of formula VI can also be carried out in the absence of a base, whereas the same condensation reaction with compounds of formula VIa or VIb (instead of a compound of formula VI) is advantageously carried out in the presence of a base (in an equimolar amount).

The condensation of the halocarbonylketenes of formula X with a hydrazine derivative of formula VI or a salt thereof of formula VIa or VIb to form compounds of formula III is carried out in a manner analogous to that described, for example, in WO 97/02243, optionally in an organic solvent, such as, for example, toluene or xylene and in the presence of a base, such as an alkaline earth metal carbonate, pyridine or triethylamine, at temperatures of from -20°C to 250°C.

If the starting materials employed are not enantiomerically pure, the compounds of formula III obtained in the above-described process are generally in the form of racemates or diastereoisomeric mixtures which, if desired, can be separated on the basis of their physicochemical properties according to known methods, such as, for example, fractional crystallisation following salt formation with optically pure bases, acids or metal complexes, or by chromatographic procedures, such as, for example, high-pressure liquid chromatography (HPLC) on acetyl cellulose.

Depending on the substituents R_0 to R_5 and G, the compounds of formula III may be in the form of geometric and/or optical isomers and isomeric mixtures (atropisomers) or as tautomers and tautomeric mixtures.

The compounds of formulae VI, VIa and VIb either are known or can be prepared analogously to known methods as described, for example, in WO 95/00521 and WO 99/47525. The alcohols of formula VII are known.

The Examples that follow further illustrate the invention without limiting it.

Preparation Examples:

Example P1: Preparation of 2,6-diethyl-4-methylbromobenzene

A solution of 8.83 g (0.128 mol) of sodium nitrite in 200 ml of water is added dropwise, at 4°C, within a period of 4 hours, to a suspension of 20 g (0.1225 mol) of 2,6-diethyl-4-methylaniline in 500 ml of 48 % hydrobromic acid and the brown solution is then heated to 80°C. After stirring for one hour at that temperature, the reaction mixture is cooled to 20°C, diluted with 1 litre of water and extracted 3 times with hexane. The combined organic phases are washed twice with brine, dried over sodium sulfate and concentrated *in vacuo* at 60°C. 27.5 g of crude product are obtained, purification of which by silica gel chromatography (500 g of silica gel; eluant: hexane) yields 19.89 g (71 % of theory) of the desired target compound in the form of a colourless oil. ^{1}H-NMR ($CDCl_3$): 6.89 ppm (s, 2H); 2.75 ppm (q, 4H); 2.27 ppm (s, 3H); 1.22 ppm (t, 6H).

Example P2: Preparation of 2,6-diethyl-4-methyliodobenzene

100 g of 4-methyl-2,6-diethylaniline and then 480 g of ice are added to a solution of 91.4 ml of sulfuric acid in 370 ml of water. To the resulting reaction solution there are added drop-

wise, at from 0 to 5°C, a solution of 44.6 g of sodium nitrite in 110 ml of water within a period of 45 minutes and, subsequently, a solution of 136.4 g of potassium iodide in 150 ml of water. After stirring for 15 hours at 20°C, the reaction mixture is extracted 3 times with a total of 3 litres of tert-butyl methyl ether (TBME); the combined organic phases are washed once with 8 % hydrochloric acid and water, dried and concentrated. 137.75 g of crude product are obtained, purification of which by distillation (boiling point 125°C/5 mbar) yields 57.8 g of the desired target compound in the form of a colourless liquid. ^{1}H-NMR ($CDCl_3$): 6.90 ppm (s, 2H); 2.75 ppm (q, 4H); 2.30 ppm (s, 3H); 1.23 ppm (t, 6H).

Example P3: Preparation of 4-methylphenylmalonic acid dinitrile

0.18 g of malonic acid dinitrile is dissolved in 15 ml of xylene and 0.72 g of sodium tert-butanolate is slowly added dropwise to the resulting solution. The yellow suspension formed is stirred at 20°C for 1 hour. 0.43 g of 4-bromotoluene and 0.035 g of bis(triphenyl-phosphine)palladium(II) dichloride ($Pd(PPh_3)_2Cl_2$) are then added and further stirring is carried out overnight at an external temperature of 150°C. For working-up, 25 ml of water and 25 ml of 1N hydrochloric acid are then added to the reaction mixture and extraction with diethyl ether is carried out. The combined ether phases are dried over sodium sulfate and concentrated. 0.72 g of crude product is obtained; its content of desired title compound is determined as 54 % by HPLC (high-pressure liquid chromatography on Nucleosil; eluant: acetonitrile/water + 0.1 % trifluoroacetic acid (TFA)), resulting in a yield of pure compound of 97 % of theory.

Example P4: Preparation of 4-methylphenylmalonic acid dinitrile

0.18 g of malonic acid dinitrile is dissolved in 13 ml of xylene, and 0.72 g of sodium tert-butanolate is slowly added dropwise to the resulting solution. The yellow suspension formed is stirred at 20°C for 1 hour. 0.43 g of 4-bromotoluene and 0.2 ml of a concentrated hydrochloric acid solution of 20 % palladium(II) dichloride ($PdCl_2$) in DMA (about 0.01 mol), and 65 g of triphenylphosphine (PPh_3) in 2 ml of xylene are then added. The yellow suspension is stirred overnight at an external temperature of 150°C. For working-up, 25 ml of water and 25 ml of 1N hydrochloric acid are then added to the reaction mixture and extraction with diethyl ether is carried out. The combined ether phases are dried over sodium sulfate and concentrated. 0.91 g of crude product is obtained; its content of desired title compound is determined as 40.5 % by HPLC (Nucleosil; eluant: acetonitrile/water + 0.1 % trifluoroacetic acid (TFA)), resulting in a yield of pure compound of 97 % of theory.

Example P5: Preparation of 2,4,6-trimethylphenylmalonic acid dinitrile

13.2 g of malonic acid dinitrile are dissolved in 500 ml of tetrahydrofuran, and 12 g of sodium hydride (NaH, 60 %) are slowly added to the resulting solution. The yellow suspension formed is stirred at 20°C for 1 hour. 25 g of 2,4,6-mesityl iodide and 0.738 g of palladium(II)-bis(tricyclohexylphosphine) dichloride ($Pd(PCy_3)_2Cl_2$) are then added and the yellow suspension is further stirred overnight at an external temperature of 80°C. For working-up, 500 ml of water and 500 ml of 1N hydrochloric acid are then added to the reaction mixture and extraction with diethyl ether is carried out. The combined ether phases are dried over sodium sulfate and concentrated. 32.2 g of crude product are obtained. Purification is carried out by silica gel chromatography (eluant: ethyl acetate/hexane 1/10) and yields 16 g (86 % of theory) of the desired title compound.

Example P6: Preparation of 2,6-diethyl-4-methylphenylmalonic acid dinitrile

0.66 g of malonic acid dinitrile is dissolved in 30 ml of tetrahydrofuran, and 0.6 g of sodium hydride (60 %) is slowly added to the resulting solution. The yellow suspension formed is stirred at 20°C for 1 hour. 1.46 g of 2,6-diethyl-4-methyliodobenzene and 0.11 g of palladium(II)-bis(tricyclohexylphosphine) dichloride ($Pd(PCy_3)_2Cl_2$)) are then added and the yellow suspension is further stirred overnight at an external temperature of 80°C. For working-up, 25 ml of water and 25 ml of 1N hydrochloric acid are then added to the reaction mixture and extraction with diethyl ether is carried out. The combined ether phases are dried over sodium sulfate and concentrated. 1.9 g of crude product are obtained. Purification is carried out by silica gel chromatography (eluant: ethyl acetate/hexane 1/10) and yields 0.62 g (58 % of theory) of the desired title compound. ^{1}H-NMR ($CDCl_3$): 7.05 ppm (s, 2H); 5.32 ppm (s, 1H); 2.85 ppm (q, 4H); 2.37 ppm (s, 3H); 1.35 ppm (t, 6H).

Example P7: Preparation of 2,6-diethyl-4-methylphenylmalonic acid dinitrile

0.66 g of malonic acid dinitrile is dissolved in 30 ml of dimethyl sulfoxide (DMSO), and 0.6 g of sodium hydride (60 %) is slowly added to the resulting solution. The yellow suspension formed is stirred at 20°C for 1 hour. 1.18 g of 2,6-diethyl-4-methylbromobenzene and 0.07 g of palladium(II)-bis(tricyclohexylphosphine) dichloride ($Pd(PCy_3)_2Cl_2$) are then added and the yellow suspension is further stirred overnight at an external temperature of 150°C. For working-up, 25 ml of water and 25 ml of 1N hydrochloric acid are then added to the reaction mixture and extraction with diethyl ether is carried out. The combined ether phases are

dried over sodium sulfate and concentrated. 1.5 g of crude product are obtained. Purification is carried out by silica gel chromatography (eluant: ethyl acetate/hexane 1/10) and yields 0.88 g (83 % of theory) of the desired title compound.

Example P8: Preparation of 2,6-diethyl-4-methylphenylmalonic acid dinitrile

0.18 g of malonic acid dinitrile is dissolved in 15 ml of xylene, and 0.72 g of sodium tert-butanolate is added to the resulting solution. The yellow suspension formed is stirred at 20°C for 1 hour. 0.59 g of 2,6-diethyl-4-methylbromobenzene and 0.035 g of bis(triphenyl-phosphine)palladium(II) dichloride ($Pd(PPh_3)_2Cl_2$) are then added and the yellow suspension is further stirred overnight at an external temperature of 150°C. For working-up, 25 ml of water and 25 ml of 1N hydrochloric acid are then added to the reaction mixture and extraction with diethyl ether is carried out. The combined ether phases are dried over sodium sulfate and concentrated. 0.92 g of crude product is obtained. Purification is carried out by silica gel chromatography (eluant: ethyl acetate/hexane 1/10) and yields 0.47 g (89 % of theory) of the desired title compound.

Example P9: Preparation of 4-bromo-2,6-diethylaniline

27 ml (0.5 mol) of bromine in 50 ml of glacial acetic acid are added dropwise, at 10°C, to a solution of 74.6 g (0.5 mol) of 2,6-diethylaniline in 200 ml of glacial acetic acid. Stirring is carried out at 20°C for 1 hour to complete the reaction; the reaction mixture is poured into an ice/water mixture, is rendered alkaline with sodium hydroxide solution and is extracted twice with ethyl acetate. The combined organic phases are washed with sodium thiosulfate solution and with brine, dried over sodium sulfate and concentrated. 112.4 g of crude oil are obtained, purification of which by distillation (boiling point 129-131°C/1 mbar) yields 92 g (81 % of theory) of the desired target compound in the form of an oil.
^{1}H-NMR ($CDCl_3$): 7.07 ppm (s, 2H); 3.60 ppm (broad signal, 2H); 2.50 ppm (q, 4H); 1.25 ppm (t, 6H).

Example P10: Preparation of 4-phenyl-2,6-diethylaniline

912 mg (0.004 mol) of 4-bromo-2,6-diethylaniline, 732 mg (0.006 mol) of phenylboric acid and 1820 mg (0.012 mol) of caesium fluoride (CsF) are placed in 20 ml of degassed dioxane, and a solution of 18 mg (0.00008 mol) of $Pd(OAc)_2$ and 47 mg (0.00012 mol) of (2'-dicyclohexylphosphanylbiphenyl-2-yl)dimethylamine in 1 ml of dioxane is added; stirring is carried out at 20°C for 16 hours. The reaction mixture is poured into dilute sodium

hydroxide solution and is extracted twice with ethyl acetate. The organic phases are washed with brine, dried over sodium sulfate and concentrated. 1.0 g of crude oil is obtained, which is chromatographed over silica gel, resulting in a yield of pure compound of 742 mg (82 % of theory) of an oil.

^{1}H-NMR ($CDCl_3$): 7.55 ppm (m, 2H); 7.39 ppm (m, 2H); 7.25 ppm (m, 1H); 7.21 ppm (s, 2H); 3.70 ppm (broad signal, 2H); 2.60 ppm (q, 4H); 1.28 ppm (t, 6H).

Example P11: Preparation of 1,4-dibromo-2,6-diethylbenzene

5.7 g (0.025 mol) of 4-bromo-2,6-diethylaniline are placed in 10 ml of water and 10 ml of 48 % hydrobromic acid, and 5.25 ml (0.02625 mol) of a 5 molar sodium nitrite solution are added dropwise at about 0°C. Stirring is carried out in an ice bath for 30 minutes and then at 100°C for 45 minutes. The reaction mixture is diluted with water and extracted twice with ethyl acetate. The organic phases are washed with brine, dried over sodium sulfate and concentrated. 6.48 g of a crude oil are obtained, yielding, after chromatography over silica gel, 3.62 g (50 % of theory) of the desired product in the form of an oil.

^{1}H-NMR ($CDCl_3$): 7.20 ppm (s, 2H); 2.75 ppm (q, 4H); 1.22 ppm (t, 6H).

Example P12: Preparation of 4-(2-pyridyl)-1-bromo-2,6-diethylbenzene

790 mg (0.005 mol) of 2-bromopyridine are placed in 7 ml of tetrahydrofuran at -70°C, and 6.7 ml (0.010 mol) of a 1.5 molar solution of tert-butyllithium in pentane are added dropwise. Stirring is carried out in a CO_2 bath for 15 minutes; a solution of 1.12 g (0.005 mol) of zinc bromide in 8 ml of tetrahydrofuran is then added dropwise and the batch is stirred without further cooling. Then, at 20°C, 1.46 g (0.005 mol) of 1,4-dibromo-2,6-diethylbenzene and 288 mg (0.00025 mol) of tetrakis(triphenylphenylphosphine)palladium(0) are added and then the batch is stirred at a bath temperature of 60°C for 1.5 hours. The reaction mixture is poured onto saturated ammonium chloride solution and extracted twice with ethyl acetate. The combined organic phases are washed with brine, dried over sodium sulfate and concentrated. 1.79 g of crude oil are obtained, yielding, after chromatography over silica gel, 700 mg (48 % of theory) of the desired title compound in the form of an oil.

^{1}H-NMR ($CDCl_3$): 7.74 ppm (m, 2H); 7.70 ppm (s, 2H); 7.23 ppm (m, 1H); 2.87 ppm (q, 4H); 1.30 ppm (t, 6H).

Example P13: Preparation of 4-phenyl-1-bromo-2,6-diethylbenzene (4-bromo-3,5-diethyl-biphenyl)

609 mg (0.0027 mol) of 4-phenyl-2,6-diethylaniline are emulsified in 2 ml of water and, at 0°C, 2 ml of hydrogen bromide solution (48 %) are added. 0.568 ml (0.002842 mol) of 5 molar sodium nitrite solution is then added thereto and stirring is carried out in an ice bath for 30 minutes and then at 100°C for 45 minutes. The reaction mixture is cooled, diluted with ice-water and extracted twice with ethyl acetate. The combined organic phases are washed with water and brine, dried over sodium sulfate and concentrated. 730 mg of a crude product are obtained, yielding, after chromatography over silica gel, the desired target compound, having a melting point of 72-74°C, in a yield of 347 mg (44 % of theory). ^{1}H-NMR ($CDCl_3$): 7.58 ppm (m, 2H); 7.43 ppm (m, 2H); 7.35 ppm (m, 1H); 7.28 ppm (s, 2H); 2.87 ppm (q, 4H); 1.28 ppm (t, 6H).

Example P14: Preparation of 2,6-diethyl-4-phenylphenylmalonic acid dinitrile

84 mg (0.00128 mol) of malonic acid dinitrile are dissolved in 7 ml of degassed xylene, 84 mg (0.00349 mol) of sodium tert-butanolate are added and stirring is carried out at 20°C for 30 minutes. 336 mg (0.00116 mol) of 4-phenyl-1-bromo-2,6-diethylbenzene and 16.3 mg (0.0000232 mol) of bis(triphenylphosphine)palladium(II) dichloride are then added and stirring is carried out at 150°C for 17 hours. The reaction mixture is poured into ice-water acidified with hydrochloric acid and is extracted twice with ethyl acetate. The combined organic phases are washed with water and brine, dried over sodium sulfate and concentrated. The desired title compound is obtained in a yield of 315 mg (99 % of theory). ^{1}H-NMR ($CDCl_3$): 7.35-7.50 ppm (m, 3H); 7.40 ppm (s, 2H); 5.35 ppm (s, 1H); 2.93 ppm (q, 4H); 1.39 ppm (t, 6H).

Analogously to the Examples hereinbefore, the following compounds (Examples P15 and P16) are also obtained:

2,6-diethyl-4-(2-pyridyl)-phenylmalonic acid dinitrile, ^{1}H-NMR ($CDCl_3$): 8.72 ppm (m, 1H); 7.82 ppm (s, 2H); 7.77 ppm (m, 2H); 7.28 ppm (m, 1H); 5.37 ppm (s, 1H); 2.95 ppm (q, 4H); 1.41 ppm (t, 6H), and

2,6-dimethyl-4-(4-pyridyl)-phenylmalonic acid dinitrile, ^{1}H-NMR ($CDCl_3$): 8.70 ppm (d, 2H); 7.47 ppm (d, 2H); 7.40 ppm (s, 2H); 5.39 ppm (s, 1H); 2.64 ppm (s, 6H).

Example P17: Preparation of 2,6-diethyl-4-methyl-phenyl-malonic acid dinitrile

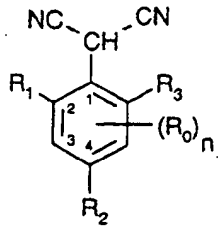
198.8 g (2.06 mol) of sodium tert-butanolate and 600 ml of xylene are placed in a 2.5 litre sulfonation flask having an internal thermometer, argon gas connection and reflux condenser or distillation head and then, at 60°C, a melt of 50.4 g (0.76 mol) of malonic acid dinitrile is added to the resulting solution, the reaction temperature increasing to 103°C. About 50 ml of the tert-butanol formed are distilled off at 80°C within a period of 70 minutes under a gentle stream of argon gas and then 496 g of 2,6-diethyl-4-methylbromobenzene (31.4 % in xylene) are added at the same temperature. The reaction solution is then heated at 130°C for 2 hours.

At the same time, 1.98 g of tricyclohexylphosphine are placed in a separate 100 ml round-bottom flask under argon gas; a mixture of 35 ml of dry xylene and 27 ml of N,N-dimethyl acetamide (DMA) is introduced by syringe and the resulting solution is degassed. 0.73 g of a 20 % palladium(II) chloride solution (conc. hydrochloric acid) is then added by syringe and the resulting yellow suspension is stirred at 20°C for 1 hour. The catalyst solution prepared in that manner is introduced into the above reaction solution at 105°C by syringe and the suspension formed is then stirred at from 120 to 130°C for 2 hours. A sample analysed by gas chromatography shows 100 % reaction without by-products or starting materials.

For working-up, the reaction mixture is cooled to 40°C and 800 ml of ice/water mixture are added. The aqueous phase (about 1.4 litres) is separated off and 365 ml of water/xylene mixture are distilled off using a rotary evaporator. The aqueous phase is then cooled further to 15°C and subsequently 142 g of 32 % hydrochloric acid solution are added so that the pH-value is from 5 to 5.5. The crystalline crude product precipitates out and can readily be filtered off and then washed with 250 ml of water. The resulting 163 g (112 % of theory) of crude product are dried overnight in a vacuum drying cabinet at 60°C, yielding 143.8 g (99 % of theory) of the desired title compound having a purity of 98.8 %.

What is claimed is:

1. A compound of formula I



(I)

wherein

R_0 is, each independently of any other, halogen, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6haloalkyl, cyano-C_1-C_6alkyl, C_2-C_6haloalkenyl, cyano-C_2-C_6alkenyl, C_2-C_6haloalkynyl, cyano-C_2-C_6alkynyl, hydroxy, hydroxy-C_1-C_6alkyl, C_1-C_6alkoxy, nitro, amino, C_1-C_6alkylamino, di(C_1-C_6alkyl)amino, C_1-C_6alkylcarbonylamino, C_1-C_6alkylsulfonylamino, C_1-C_6alkylaminosulfonyl, C_1-C_6alkylcarbonyl, C_1-C_6alkylcarbonyl-C_1-C_6alkyl, C_1-C_6alkoxycarbonyl-C_1-C_6alkyl, C_1-C_6alkylcarbonyl-C_2-C_6alkenyl, C_1-C_6alkoxycarbonyl, C_1-C_6alkoxycarbonyl-C_2-C_6alkenyl, C_1-C_6alkylcarbonyl-C_2-C_6alkynyl, C_1-C_6alkoxycarbonyl-C_2-C_6alkynyl, cyano, carboxyl, phenyl or an aromatic ring that contains 1 or 2 hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein the latter two aromatic rings may be substituted by C_1-C_3alkyl, C_1-C_3haloalkyl, C_1-C_3alkoxy, C_1-C_3haloalkoxy, halogen, cyano or by nitro; or

R_0, together with the adjacent substituents R_1, R_2 and R_3, forms a saturated or unsaturated C_3-C_6hydrocarbon bridge that may be interrupted by 1 or 2 hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur and/or substituted by C_1-C_4alkyl;

R_1, R_2 and R_3 are, each independently of the others, hydrogen, halogen, C_1-C_6alkyl, C_2-C_6-alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, C_1-C_6haloalkyl, C_2-C_6haloalkenyl, C_1-C_6alkoxy-carbonyl-C_2-C_6alkenyl, C_1-C_6alkylcarbonyl-C_2-C_6alkenyl, cyano-C_2-C_6alkenyl, nitro-C_2-C_6-alkenyl, C_2-C_6haloalkynyl, C_1-C_6alkoxycarbonyl-C_2-C_6alkynyl, C_1-C_6alkylcarbonyl-C_2-C_6-alkynyl, cyano-C_2-C_6alkynyl, nitro-C_2-C_6alkynyl, C_3-C_6halocycloalkyl, hydroxy-C_1-C_6alkyl, C_1-C_6alkoxy-C_1-C_6alkyl, C_1-C_6alkylthio-C_1-C_6alkyl, cyano, C_1-C_4alkylcarbonyl, C_1-C_6-alkoxycarbonyl, hydroxy, C_1-C_{10}alkoxy, C_3-C_6alkenyloxy, C_3-C_6alkynyloxy, C_1-C_6haloalkoxy, C_3-C_6haloalkenyloxy, C_1-C_6alkoxy-C_1-C_6alkoxy, mercapto, C_1-C_6alkylthio, C_1-C_6haloalkylthio, C_1-C_6alkylsulfinyl, C_1-C_6alkylsulfonyl, nitro, amino, C_1-C_6alkylamino, di(C_1-C_6alkyl)amino or

phenoxy in which the phenyl ring may be substituted by C_1-C_3alkyl, C_1-C_3haloalkyl, C_1-C_3-alkoxy, C_1-C_3haloalkoxy, halogen, cyano or by nitro;

R_2 also may be phenyl, naphthyl or a 5- or 6-membered aromatic ring that may contain 1 or 2 hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein the phenyl ring, the naphthyl ring system and the 5- or 6-membered aromatic ring may be substituted by halogen, C_3-C_8cycloalkyl, hydroxy, mercapto, amino, cyano, nitro or by formyl; and/or

the phenyl ring, the naphthyl ring system and the 5- or 6-membered aromatic ring may be substituted by C_1-C_6alkyl, C_1-C_6alkoxy, hydroxy-C_1-C_6alkyl, C_1-C_6alkoxy-C_1-C_6alkyl, C_1-C_6-alkoxy-C_1-C_6alkoxy, C_1-C_6alkylcarbonyl, C_1-C_6alkylthio, C_1-C_6alkylsulfinyl, C_1-C_6alkylsulfonyl, mono-C_1-C_6alkylamino, di(C_1-C_6alkyl)amino, C_1-C_6alkylcarbonylamino, C_1-C_6alkylcarbonyl-(C_1-C_6alkyl)amino, C_2-C_6alkenyl, C_3-C_6alkenyloxy, hydroxy-C_3-C_6alkenyl, C_1-C_6alkoxy-C_2-C_6-alkenyl, C_1-C_6alkoxy-C_3-C_6alkenyloxy, C_2-C_6alkenylcarbonyl, C_2-C_6alkenylthio, C_2-C_6alkenyl-sulfinyl, C_2-C_6alkenylsulfonyl, mono- or di-(C_2-C_6alkenyl)amino, C_1-C_6alkyl(C_3-C_6alkenyl)-amino, C_2-C_6alkenylcarbonylamino, C_2-C_6alkenylcarbonyl(C_1-C_6alkyl)amino, C_2-C_6alkynyl, C_3-C_6alkynyloxy, hydroxy-C_3-C_6alkynyl, C_1-C_6alkoxy-C_3-C_6alkynyl, C_1-C_6alkoxy-C_4-C_6-alkynyloxy, C_2-C_6alkynylcarbonyl, C_2-C_6alkynylthio, C_2-C_6alkynylsulfinyl, C_2-C_6alkynylsulfonyl, mono- or di-(C_3-C_6alkynyl)amino, C_1-C_6alkyl(C_3-C_6alkynyl)amino, C_2-C_6alkynylcarbonylamino or by C_2-C_6alkynylcarbonyl(C_1-C_6alkyl)amino; and/or

the phenyl ring, the naphthyl ring system and the 5- or 6-membered aromatic ring may be substituted by halo-substituted C_1-C_6alkyl, C_1-C_6alkoxy, hydroxy-C_1-C_6alkyl, C_1-C_6alkoxy-C_1-C_6alkyl, C_1-C_6alkoxy-C_1-C_6alkoxy, C_1-C_6alkylcarbonyl, C_1-C_6alkylthio, C_1-C_6alkylsulfinyl, C_1-C_6alkylsulfonyl, mono-C_1-C_6alkylamino, di(C_1-C_6alkyl)amino, C_1-C_6alkylcarbonylamino, C_1-C_6alkylcarbonyl(C_1-C_6alkyl)amino, C_2-C_6alkenyl, C_3-C_6alkenyloxy, hydroxy-C_3-C_6alkenyl, C_1-C_6alkoxy-C_2-C_6alkenyl, C_1-C_6alkoxy-C_3-C_6alkenyloxy, C_2-C_6alkenylcarbonyl, C_2-C_6-alkenylthio, C_2-C_6alkenylsulfinyl, C_2-C_6alkenylsulfonyl, mono- or di-(C_2-C_6alkenyl)amino, C_1-C_6-alkyl(C_3-C_6alkenyl)amino, C_2-C_6alkenylcarbonylamino, C_2-C_6alkenylcarbonyl(C_1-C_6-alkyl)amino, C_2-C_6alkynyl, C_3-C_6alkynyloxy, hydroxy-C_3-C_6alkynyl, C_1-C_6alkoxy-C_3-C_6alkynyl, C_1-C_6alkoxy-C_4-C_6alkynyloxy, C_2-C_6alkynylcarbonyl, C_2-C_6alkynylthio, C_2-C_6alkynylsulfinyl, C_2-C_6alkynylsulfonyl, mono- or di-(C_3-C_6alkynyl)amino, C_1-C_6alkyl(C_3-C_6alkynyl)amino, C_2-C_6alkynylcarbonylamino or C_2-C_6alkynylcarbonyl(C_1-C_6alkyl)amino; and/or

the phenyl ring, the naphthyl ring system and the 5- or 6-membered aromatic ring may be substituted by a radical of formula $COOR_{50}$, $CONR_{51}$, $SO_2NR_{53}R_{54}$ or SO_2OR_{55}, wherein R_{50}, R_{51}, R_{52}, R_{53}, R_{54} and R_{55} are, each independently of the others, C_1-C_6alkyl, C_2-C_6alkenyl or

C_3-C_6alkynyl or halo-, hydroxy-, alkoxy-, mercapto-, amino-, cyano-, nitro-, alkylthio-, alkylsulfinyl- or alkylsulfonyl-substituted C_1-C_6alkyl, C_2-C_6alkenyl or C_3-C_6alkynyl; and n is 0, 1 or 2.

2. A compound according to claim 1, wherein R_0 is, each independently of any other, halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, hydroxy, C_1-C_6alkoxy, nitro, amino, C_1-C_6alkylamino, di-(C_1-C_6alkyl)amino, C_1-C_6alkylcarbonylamino, C_1-C_6alkylsulfonylamino, C_1-C_6alkylamino-sulfonyl, C_1-C_4alkylcarbonyl, C_1-C_6alkoxycarbonyl or carboxyl; and R_1, R_2 and R_3 are, each independently of the others, hydrogen, halogen, C_1-C_6alkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, C_3-C_6cycloalkyl, C_1-C_6-haloalkyl, C_2-C_6haloalkenyl, C_2-C_6haloalkynyl, C_3-C_6halocycloalkyl, C_1-C_6alkoxy-C_1-C_6alkyl, C_1-C_6alkylthio-C_1-C_6alkyl, cyano, C_1-C_4alkylcarbonyl, C_1-C_6alkoxy-carbonyl, hydroxy, C_1-C_{10}alkoxy, C_3-C_6alkenyloxy, C_3-C_6alkynyloxy, C_1-C_6haloalkoxy, C_3-C_6-haloalkenyloxy, C_1-C_6alkoxy-C_1-C_6alkoxy, mercapto, C_1-C_6alkylthio, C_1-C_6haloalkylthio, C_1-C_6alkylsulfinyl, C_1-C_6alkylsulfonyl, nitro, amino, C_1-C_4alkylamino or di(C_1-C_4alkyl)amino.

3. A compound according to claim 2, wherein R_1, R_2 and R_3 are, each independently of the others, hydrogen, halogen, C_1-C_4alkyl, C_1-C_4haloalkyl, C_2-C_4alkenyl, C_2-C_4haloalkenyl, C_2-C_4alkynyl, C_3-C_6cycloalkyl, C_1-C_4alkylcarbonyl, C_1-C_6alkoxycarbonyl, hydroxy, C_1-C_4-alkoxy, C_3- or C_4-alkenyloxy, C_3- or C_4-alkynyloxy, C_1-C_4haloalkoxy, nitro or amino.

4. A compound according to claim 1, wherein R_1 is C_2-C_6alkyl.

5. A compound according to claim 1, wherein n is 0.

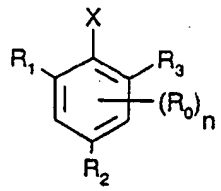
6. A compound according to claim 5, wherein R_1 is C_2-C_4alkyl, C_1-C_4alkoxy, C_2-C_4alkynyl or C_3-C_6cycloalkyl and R_3 is C_1-C_4alkyl, C_1-C_4alkoxy, C_2-C_4alkynyl or C_3-C_6cycloalkyl.

7. A compound according to claim 1, wherein R_1 is C_2-C_6alkynyl.

8. A compound according to claim 1, wherein R_1 and R_3 are, each independently of the other, C_2-C_6alkyl, C_2-C_6alkynyl, C_1-C_{10}alkoxy or C_3-C_6cycloalkyl.

9. A compound according to claim 8, wherein R_1 is C_2-C_6alkyl and R_3 is C_2-C_6alkyl, C_2-C_6-alkynyl or C_1-C_{10}alkoxy.

10. A process for the preparation of a compound of formula I according to claim 1, which comprises reacting a compound of formula II



(II),

wherein R_0, R_1, R_2, R_3 and n are as defined in claim 1 and X is a leaving group, with the malonic acid dinitrile anion in an inert solvent in the presence of a palladium catalyst.

11. A process according to claim 10, wherein in the compound of formula II X is halogen, $R_{10}S(O)_2O$- (wherein R_{10} is methyl, halomethyl, n-C_4F_9, phenyl or phenyl mono- to tri-substituted by halogen, methyl or by halomethyl) or mono-, di- or tri-arylmethoxy.

12. A process according to claim 11, wherein X is chlorine, bromine, iodine, $CF_3S(O)_2O$- (triflate), $CF_3(CF_2)_3S(O)_2O$- (nonaflate), p-tolyl-$S(O)_2O$- (tosylate), $(C_6H_5)_2CHO$-, $(CH_3$-$C_6H_4)_2CHO$-, $(C_6H_5)_3CO$- (trityl) or $(CH_3$-$C_6H_4)_3CO$-.

13. A process according to claim 12, wherein X is chlorine, bromine or iodine.

14. A process according to claim 10, wherein a palladium(II) or palladium(0) complex is used as palladium catalyst.

15. A process according to claim 14, wherein a palladium(II) dihalide, palladium(II) acetate, palladium(II) sulfate, bis(triphenylphosphine)palladium(II) dichloride, bis(tricyclopentylphosphine)palladium(II) dichloride, bis(tricyclohexylphosphine)palladium(II) dichloride, bis(dibenzylideneacetone)palladium(0) or tetrakis(triphenylphosphine)palladium(0) is used as palladium catalyst.

16. A process according to claim 10, wherein the palladium catalyst is prepared 'in situ' from a palladium(II) or palladium(0) compound by complexing with the desired ligand.

17. A process according to claim 10, wherein the palladium catalyst is used in an amount of from 0.001 to 50 mol %, preferably from 0.01 to 10 mol % and especially from 0.1 to 3 mol %, based on the compound of formula II.

18. A process according to claim 10, wherein an aliphatic, cycloaliphatic or aromatic hydrocarbon, aliphatic halohydrocarbon, nitrile, ether, alcohol, ketone, ester or lactone, N-substituted lactam, amide, acyclic urea, sulfoxide or a mixture of these solvents is used as solvent.

19. A process according to claim 18, wherein an aromatic hydrocarbon, an ether or dimethyl sulfoxide is used.

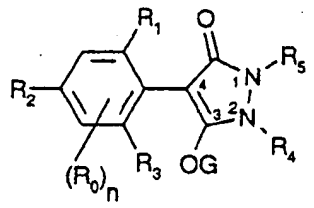
20. A process according to claim 10, wherein a tri-alkali metal phosphate, alkali metal or alkaline earth metal hydride, alkali metal or alkaline earth metal amide, or alkali metal alcoholate is used as the base.

21. A process according to claim 20, wherein the base is used in an equivalent amount or in an excess of from 2 to 10 equivalents, based on malonic acid dinitrile.

22. A process according to claim 10, wherein the formation of the malonic acid dinitrile anion is carried out at a temperature of from 0° to 100°C and the reaction thereof with the compound of formula II is carried out at a reaction temperature of from 30° to 250°C.

23. A process according to claim 10, wherein the reaction of the malonic acid dinitrile anion with a compound of formula II is carried out at an elevated pressure of from 1.1 to 10 bar.

24. The use of a compound of formula I according to claim 1 as an intermediate in the preparation of a substituted 3-hydroxy-4-aryl-5-oxopyrazoline derivative of formula III

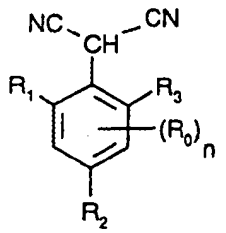


(III),

wherein R_0, R_1, R_2, R_3 and n are as defined in claim 1, and R_4 and R_5 are, each independently of the other, hydrogen, C_1-C_{12}alkyl, C_1-C_{12}haloalkyl, C_2-C_8alkenyl, C_2-C_8-alkynyl, C_1-C_{10}alkoxy-C_1-C_8alkyl, poly-C_1-C_{10}alkoxy-C_1-C_8alkyl, C_1-C_{10}alkylthio-C_1-C_8alkyl, C_3-C_8cycloalkyl, C_3-C_8halocycloalkyl, 4- to 8-membered heterocyclyl, phenyl, α- or β-naphthyl, phenyl-C_1-C_6alkyl, α- or β-naphthyl-C_1-C_6alkyl, 5- or 6-membered heteroaryl or 5- or 6-membered heteroaryl-C_1-C_6alkyl, wherein the aromatic and heteroaromatic rings may be substituted by halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, nitro or by cyano, or

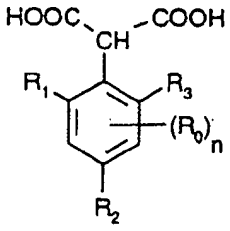
R_4 and R_5, together with the nitrogen atoms to which they are bonded, form a saturated or unsaturated, 5- to 8-membered heterocyclic ring that 1) may be interrupted by oxygen, sulfur or by -NR_7- and/or substituted by halogen, C_1-C_{10}alkyl, C_1-C_{10}haloalkyl, hydroxy, C_1-C_6alkoxy, C_1-C_6alkoxy-C_1-C_6alkoxy, C_1-C_6haloalkoxy, mercapto, C_1-C_6alkylthio, C_3-C_7cyclo-alkyl, heteroaryl, heteroaryl-C_1-C_6alkyl, phenyl, phenyl-C_1-C_6alkyl or by benzyloxy, wherein the phenyl rings of the last 3 substituents may in turn be substituted by halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy or by nitro, and/or 2) may contain a fused or spiro-bound alkylene or alkenylene chain having from 2 to 6 carbon atoms that is optionally interrupted by oxygen or by sulfur, or at least one ring atom of the saturated or unsaturated heterocyclic ring bridges that alkylene or alkenylene chain; R_7 is hydrogen, C_1-C_4alkyl, C_1-C_6alkylcarbonyl, C_1-C_6alkylsulfonyl, C_3-C_6alkenyl or C_3-C_6alkynyl; and G is hydrogen, a metal ion equivalent or an ammonium, sulfonium or phosphonium ion, which comprises either

a) hydrolysing a compound of formula I



(I),

wherein R_0, R_1, R_2, R_3 and n are as defined hereinbefore, to form a compound of formula IV



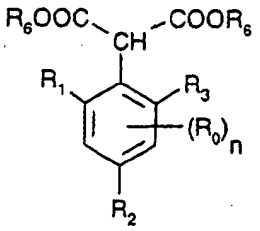
(IV),

and then, in a manner known *per se*, either

a_1) esterifying that compound with an alcohol of formula VII

R_6-OH (VII),

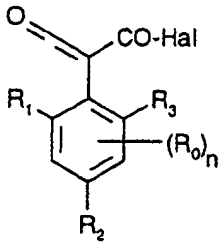
wherein R_6 is C_1-C_6alkyl, C_1-C_6haloalkyl or benzyl, to form the arylmalonic acid ester of formula V



(V),

wherein R_0, R_1, R_2, R_3, R_6 and n are as defined hereinbefore, or

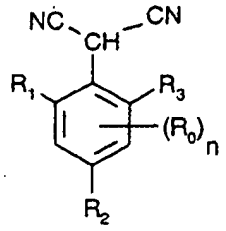
a_2) converting that compound, using an acid halide, into the halocarbonylketene of formula X



(X),

wherein R_0, R_1, R_2, R_3 and n are as defined hereinbefore and Hal is halogen, or

b) subjecting a compound of formula I

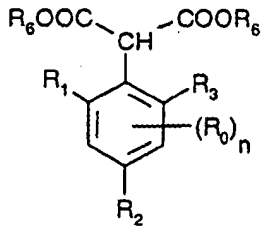


(I),

wherein R_0, R_1, R_2, R_3 and n are as defined hereinbefore, to alcoholysis directly with a compound of formula VII

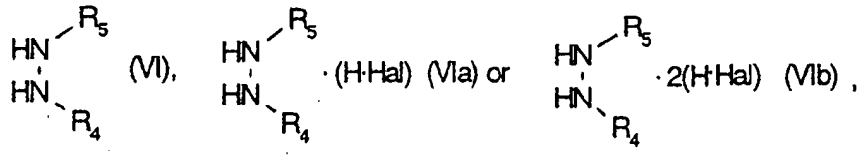
R_6-OH (VII),

wherein R_6 is as defined hereinbefore, to form a compound of formula V



(V),

wherein R_0, R_1, R_2, R_3, R_6 and n are as defined hereinbefore, and then reacting that compound of formula V or a compound of formula X with a compound of formula VI, VIa or VIb



wherein R_4 and R_5 are as defined hereinbefore and H•Hal is a hydrogen halide, in an inert organic solvent, optionally in the presence of a base, and then optionally converting the resulting compound of formula III wherein G is a metal ion equivalent or an ammonium cation, by salt conversion into the corresponding salt of formula III wherein G is a sulfonium or phosphonium cation, or by treatment with a Brönsted acid into the corresponding compound of formula III wherein G is hydrogen.

INTERNATIONAL SEARCH REPORT

Int'l Application No
PCT/EP 00/05477

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C255/33 C07C253/30 C07D213/57

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WILLAM ADCOCK AND DOUGLAS P COX: "Electronic nature of the tricyanomethyl group by 13C and 19F NMR: Nature of aryl 19F NMR polar field effects in the benzene and naphthalene ring systems" JOURNAL OF ORGANIC CHEMISTRY., vol. 44, no. 17, 1979, pages 3004-17, XP002146145 AMERICAN CHEMICAL SOCIETY. EASTON., US ISSN: 0022-3263 page 3008; examples 2,3; table 3 --- -/--	1

[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 August 2000	26/09/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	O'Sullivan, P

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INTERNATIONAL SEARCH REPORT

Int. ional Application No
PCT/EP 00/05477

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	HOWARD E ZIMMERMAN; DONALD R DIEHL: "Molecular control of excited cross-conjugated triene rearrangements. Exploratory and mechanistic organic photochemistry" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY., vol. 101, no. 7, 1979, pages 1841-57, XP002146146 AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC., US ISSN: 0002-7863 scheme II, structure 23 scheme III, structure 18 ---	1
X	IVO LEITO ET AL: "Spectrophotometric acidity scale of strong neutral bronsted acids in acetonitrile" JOURNAL OF ORGANIC CHEMISTRY., vol. 63, no. 22, 1998, pages 7868-74, XP002146147 AMERICAN CHEMICAL SOCIETY. EASTON., US ISSN: 0022-3263 table 1, numbers 3,5,6,7 ---	1-3,5
X	E B TROUGHTON ET AL: "Coordination, heterolysis, and electron transfer reactions involving delocalised carbocations and carbanions in solution" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY., vol. 106, no. 22, 1984, pages 6726-35, XP002146148 AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC., US ISSN: 0002-7863 page 6727, column 2, line 14 - line 21 ---	1,5
X	ILAMAR A KOPPEL ET AL: "The gas-phase acidities of very strong neutral bronsted acids" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY., vol. 116, no. 7, 1994, pages 3047-57, XP002146149 AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC., US ISSN: 0002-7863 table 1, examples 22,23,26,37,39,41,48,54,59,60,62,70,73 ---	1-3,5
X	WINSTON A DAVIS AND MICHAEL P CAVA: "A new synthesis of arylmalononitriles" JOURNAL OF ORGANIC CHEMISTRY., vol. 48, 1983, pages 2774-5, XP002146150 AMERICAN CHEMICAL SOCIETY. EASTON., US ISSN: 0022-3263 table 1 ---	1,5
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INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/EP 00/05477

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	RUDOLF GOMPPER AND OTTO CHRISTMANN: "Neue synthese aromatischer kohlenwasserstoffe" CHEMISCHE BERICHTE., vol. 94, 1961, pages 1795-99, XP002146151 VERLAG CHEMIE GMBH. WEINHEIM., DE ISSN: 0009-2940 page 1797, line 12	1-3
X	MARTIN R BRYCE ET AL: "New electron acceptors: Synthesis, electrochemistry, and radical anions of N,7,7-tricyanoquinometanimines and X-ray crystal structures of the trimethyl and tetramethyl derivatives" JOURNAL OF ORGANIC CHEMISTRY., vol. 57, no. 6, 1992, pages 1690-96, XP002146152 AMERICAN CHEMICAL SOCIETY. EASTON., US ISSN: 0022-3263 scheme II, structure 11	1-3
X	YOSHIAKI TSUBATA ET AL : "Single component organic conductors based on neutral radicals containing the pyrazino-TCNQ skeleton" JOURNAL OF ORGANIC CHEMISTRY., vol. 57, no. 25, 1992, pages 6749-55, XP002146153 AMERICAN CHEMICAL SOCIETY. EASTON., US ISSN: 0022-3263 page 6753, column 2, preparation of (1)	10-15, 17-22
X	M UNO ET AL: "A new route to phenylenedimalononitrile and the analogues,using palladium-catalysed carbon-carbon bond formation" TETRAHEDRON LETTERS., vol. 26, no. 12, 1985, pages 1553-6, XP002146154 ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM., NL ISSN: 0040-4039 table 1	10-15, 17-22
A	MITSUNARI UNO ET AL: "Palladium-catalysed 1,4-arylation/alkylation of buta-1,3-diene with halogenarenes and stabilised anions" JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1., 1990, pages 647-51, XP002146155 CHEMICAL SOCIETY. LETCHWORTH., GB ISSN: 0300-922X the whole document	10-23

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